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Behavioral Toxicity of Acute and Subacute Exposure to Triethyltin in the Rat

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16. ABSTRACT

Triethyltin (TET), the most toxic of the alkyltin compounds is used industrially as both a catalyst and a biocide (NIOSH, 1976). Stoner et al. (1955) determined the acute toxicity of a series of alkyltins and reported that in the rat, the LD_{50} for TET was 5.7 mg/kg. Barnes and Stoner (1958) reported that this toxicity was independent of the route of adminstration. Within 30 min. of exposure to 10 mg/kg, animals exhibited generalized weakness, especially in the hindlimbs. In more severe cases, this condition progressed to both hindlimb and forelimb paralysis.

Magee et al. (1957) reported that TET produced a striking interstital edema in the white matter of both the brain and spinal cord characterized by split myelin sheaths which were dilated and filled with fluid (spongy degeneration). The spongy degeneration produced by TET is similar to the observed in rats with hexachlorophene intoxication (Cammer et al., 1975) and has been reported in monkeys and cats (Hedges and Zaren, 1969). This effect is reversible after termination of exposure (Magee et al., 1957) and also occurs in peripheral nerves (Graham and Gonatas, 1973). TET-induced brain edema is associated with a reduction in total myelin content of the brain although the chemical compositon of the myelin is normal (Eto et al., 1971). No change in the blood-brain barrier to trypan blue has been found (Aleu et al., 1963).

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BEHAVIORAL TOXICITY OF ACUTE AND SUBACUTE EXPOSURE TO TRIETHYLTIN IN THE RAT

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The behavioral effects of both acute and subacute triethyltin (TET) exposure were examined in the rat. Animals acutely exposed to TET at doses of 0, 1.5 and 3.0 mg/kg showed a dose-related decrease in motor activity when tested between 2 and 4 hr following exposure. Subacute (3 week) exposure to TET in the drinking water (5 or 10 ppm) resulted in performance decrements in the following: maze activity, open field behavior, acoustic startle response and landing foot-spread. Early signs of behavioral deficits were observed 2 weeks after 10 ppm TET. These effects were reversible within one month after termination of exposure.

INTRODUCTION

Triethyltin (TET), the most toxic of the alkyltin compounds, is used industrially as both a catalyst and a biocide (NIOSH, 1976). Stoner *et al.* (1955) determined the acute toxicity of a series of alkyltins and reported that in the rat, the LD_{50} for TET was 5.7 mg/kg. Barnes and Stoner (1958) reported that this toxicity was independent of the route of administration. Within 30 min of exposure to 10 mg/kg, animals exhibited generalized weakness, especially in the hindlimbs. In more severe cases, this condition progressed to both hindlimb and forelimb paralysis.

Magee *et al.* (1957) reported that TET produced a striking interstitial edema in the white matter of both the brain and the spinal cord characterized by split myelin sheaths which were dilated and filled with fluid (spongy degeneration). The spongy degeneration produced by TET is similar to that observed in rats with hexachlorophene intoxication (Cammer *et al.*, 1975) and has also been reported in monkeys and cats (Hedges and Zaren, 1969). This effect is reversible after termination of exposure (Magee *et al.*, 1957) and also occurs in peripheral nerves (Graham and Gonatas, 1973). TET-induced brain edema is associated with a reduction in total myelin content of the brain

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although the chemical composition of the myelin is normal (Eto *et al.*, 1971). No change in the blood-brain barrier to trypan blue has been found (Aleu *et al.*, 1963).

Several investigators have examined the biochemical consequences of trialkyltin exposure. Stockdale *et al.* (1970) investigated a series of trialkyltins in isolated mitochondria and reported inhibition of both oxidative phosphorylation and coupled respiration. TET in a concentration of 2.5 μM inhibited glucose oxidation by 50% in rat brain cortical slices (Lock, 1976). This effect was also observed in rat brain following *in vivo* exposure (Cremer, 1970).

Although considerable research has focused on the anatomical and biochemical toxicity of TET, little consideration has been given to the behavioral consequences of TET exposure. The present series of experiments was performed to evaluate the behavioral toxicity of both acute and subacute TET exposure in adult rats. Results indicate that TET is an extremely potent behavioral toxicant producing impaired motor function and altered behavior following 3 week exposure to levels of 5 ppm in the drinking water.

MATERIALS AND METHODS

General Methods

Animals Animals were male CD rats (90-120 days of age) obtained from Charles River (Wilmington, MA). Purina Lab Chow and water were available *ad libitum* throughout all experiments. All animals were housed in groups of 3 in cages measuring 45 x 24 x 20 cm. The animal room was maintained on a 12 hr:12 hr light-dark cycle beginning at 0600 hr. All behavioral testing was conducted during the diurnal period.

Dosing Triethyltin bromide (TET, Alfa Products; Danvers, MA) was used in all experiments. For Exp. I, TET was dissolved in sterile isotonic saline and injected subcutaneously in a volume of 1.0 ml/kg. For the subacute experiments (II and III), TET was combined with 50% ethanol (by volume) to produce a stock solution of 20 mg/ml TET (as the bromide salt); a control stock solution of 50% ethanol was also prepared. Aliquots of these stock solutions were then added to tap water to provide dose levels of 0, 5, 10, 15 and 20 ppm TET in the drinking water (mg/liter).

Body weight, food and water consumption For the subacute experiments, body weights were obtained prior to exposure, and either once or twice weekly for the duration of the experiment. Water consumption was measured at weekly intervals by weighing water bottles on two consecutive days; the difference in weight was calculated as water intake. Food consumption was measured in Experiment IIIa by weighing food dishes containing ground Purina Lab Chow. Since weekly estimates of food and water consumption were made by cage, no statistical analyses of these data were performed.

Behavioral Testing

Figure-Eight Maze Motor activity was measured in a figure-eight maze as previously described (Norton *et al.*, 1975; Reiter *et al.*, 1975). Briefly, the

maze consists of a series of interconnected alleys (10 x 10 cm) converging on a central open field and covered with transparent acrylic plastic. Motor activity was detected by 8 phototransistor/photodiode pairs; one count was registered each time a light beam was interrupted. Eight mazes were housed in a sound-attenuated room maintained on a photoperiod identical to the animal quarters. In all experiments, rats were individually tested for 2 hr and were transported to the maze room 5 min prior to testing.

Open field Motor activity was also measured in a standard open field measuring 90 x 90 x 60 cm, and divided into sixteen 22.5 cm squares. Activity was measured as crossovers (counted each time an animal entered a square with all four feet) and rears (counted each time an animal raised both front paws). Testing was conducted under normal lighting, and all activity was monitored on closed-circuit television by observers in an adjacent room. Each animal was placed in the center of the open field and tested for 5 min.

Startle response Animals' response to an auditory stimulus, produced by the sudden closure of a mousetrap, was measured on a force platform (Denenberg *et al.*, 1973). Vertical force exerted on the platform was detected by a series of strain gauges. For each animal, a baseline reading was obtained as the force exerted on the platform prior to startle (i.e., body mass). The baseline was then subtracted from the force exerted at the peak of the startle response to obtain the amplitude of the startle response. Each animal was tested once.

Drop technique Animals were tested for landing foot-spread as a measure of motor function according to the procedure of Edwards and Parker (1977). The animals' hindpaws were dipped in ink, and the animal was suspended in a horizontal position 30 cm above a table. Each animal was dropped twice and the distance between the footprints produced by the hindpaws was measured; for each animal, an average of the two trials was used.

Statistical Analysis

Behavioral data were analyzed by either a univariate or a multivariate general linear model (MGLM) procedure (Morrison, 1967). *Post-hoc* comparisons were made using Tukey's T-method.

Experiment I

Experiment I was conducted to determine the effects of acute exposure to TET on motor activity in the figure-eight maze. Thirty-six male rats were assigned to 3 dose groups with 12 animals per group. TET was injected subcutaneously 2 hr prior to testing at doses of 0, 1.5 and 3.0 mg/kg.

Results

Maze counts for the total 2 hr testing period are shown in Fig. 1. Total activity counts differed significantly between treatment groups ($F(2,32) = 3.354$, $p<.046$); animals receiving the high dose of TET (3.0 mg/kg) were

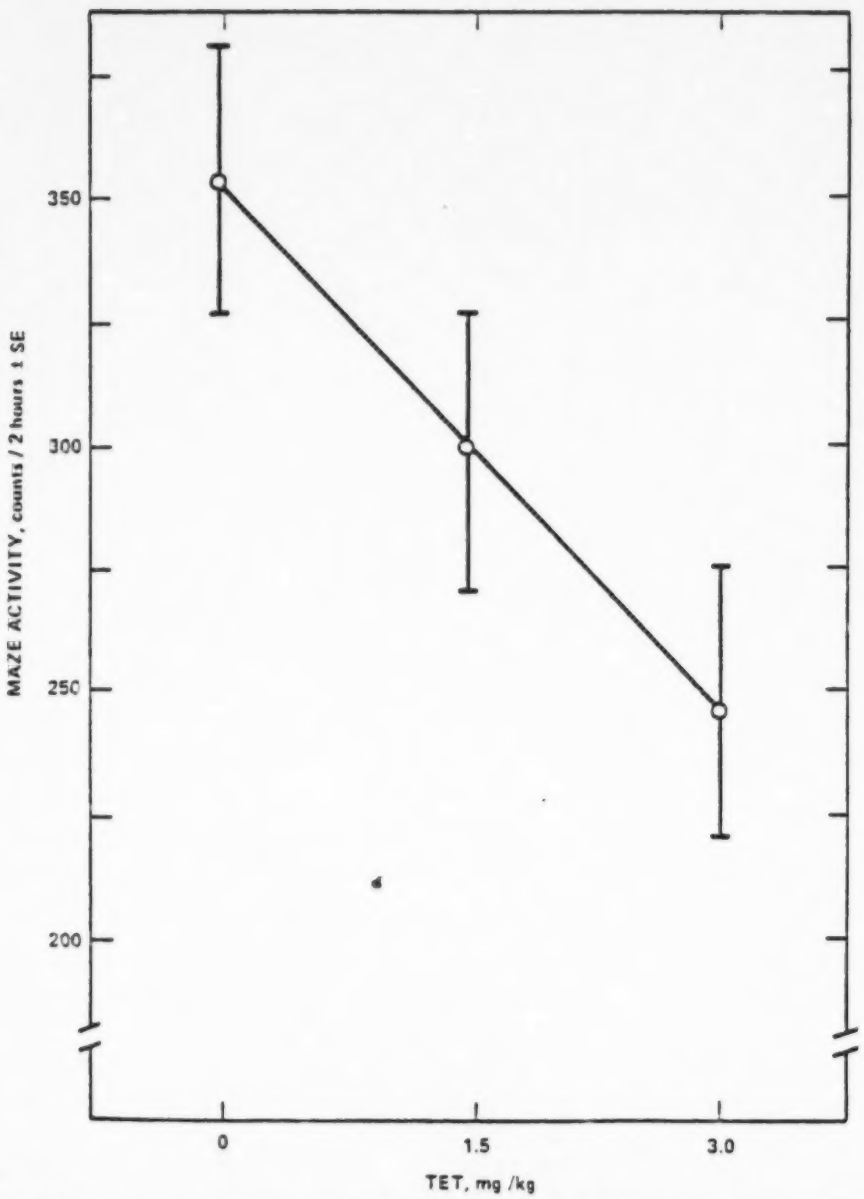

FIGURE 1. Maze activity of male rats following acute exposure to TET. Testing was performed 2 hr after sc administration. Values are expressed as means (±SE) for 12 animals/group.

significantly less active in the maze than control animals ($p<.05$). Therefore, the effect of TET was to decrease locomotor activity.

Experiment II

Experiment II was performed to assess the effects of subacute exposure to TET on behavior of adult male rats. Twenty-four rats were assigned to 4 exposure groups (N=6) that received either 0, 5, 10 or 20 ppm TET in the drinking water for 28 days. On Day 22 open field activity was measured, on Day 23 maze activity was measured and on Day 25 the startle response was measured. All animals were sacrificed one week following testing, and body weights, adrenal, brain and liver weights were obtained.

Results

Table 1 shows water consumption, body weights and both the average daily dose of TET per week and the total dose of TET for all groups throughout the first 3 weeks of TET exposure. Water intake for all TET groups was depressed according to dose, and body weight gain was reduced in the 20 ppm dose group. Animals receiving 20 ppm TET began to show signs of intoxication after the first week of exposure. Initial signs were loss of body tone and altered gait in the hindlimbs which developed into hind limb paralysis (i.e., animals would drag their hind limbs while moving) after approximately 2 weeks of exposure. These animals were not tested behaviorally.

Maze activity, magnitude of the startle reponse, and open field behavior (rears and crossovers) are shown in Fig. 2. Total maze activity (N=5/group) for the 2 hr test period differed significantly between treatment groups ($F(2,12)=10.316, p<.003$); animals receiving either 5 ppm or 10 ppm TET were less active than controls ($p<.05$). On the second test of activity, the open field, there were no differences between groups in either crossovers or rears during the 5-min test.

Because of the variability in the magnitude of the startle response in control animals, a $\log_{10}$ transformation was performed on these data. The magnitude of the startle response differed between treatment groups ($F(2,15)=7.358$, $p<.006$); animals exposed to 10 ppm TET were less reactive to the stimulus than controls ($p<.01$).

Organ weights at the time of sacrifice (adrenal, brain and liver weights) did not differ among the treatment groups (Table 2).

Because animals receiving TET showed reduced water intake, and body weight gain was reduced in the highest TET dose group (20 ppm) an additional group receiving 0.025% quinine in the drinking water was included in a control experiment to determine if reduced water consumption and weight gain in the absence of TET exposure would in itself alter maze activity. For 12 control animals and 12 animals receiving 0.025% quinine in the drinking water, food and water consumption were measured over a 3 week period, followed by a test of maze activity.

These data, shown in Table 3, indicate that water consumption was effectively reduced by quinine administration. Although body weights were

TABLE 1. Water Consumption, Body Weight, Average Daily Dose of TET per Week (Mean ± SE) and the Total Dose of TET Following Subacute Exposure in the Drinking Water (N=6 per Dose)

Exposure Level	Week	Water Consumption (ml/Rat/Day)	Body Weight (g)	Mean Daily Dose/Week (mg/kg/Day)	Total dose (mg/kg)
0 ppm	0	-	388±11	-	
	1	57±5	384±12	0	
	2	57±7	406±11	0	
	3	48±5	423±10	0	0
5 ppm	0	-	383±8	-	
	1	39±8	399±8	0.49	
	2	30±1	410±8	0.36	
	3	31±0	424±9	0.36	8.4
10 ppm	0	-	388±11	-	
	1	26±1	387±10	0.67	
	2	26±1	394±12	0.66	
	3	27±1	414±13	0.65	13.9
20 ppm	0	-	384±9	-	
	1	11±10	381±8	0.58	
	2	22±2	379±11	1.16	
	3	14±1	384±9	0.73	17.3

also reduced in animals receiving 0.025% quinine ($F(4,19)=5.58$, $p=.004$), maze activity was not significantly different from control levels. These data indicate that the decreased activity shown by TET animals cannot be accounted for by reduction in either water intake or body weight gain.

Experiment III

Experiment II demonstrated the subacute effect of TET on behavior following 3 weeks exposure. The purposes of Experiment III were: (1) to replicate the behavioral results seen in Experiment II; (2) to determine the time course for the appearance of TET effects on behavior; and (3) to determine the time course for behavioral recovery following cessation of treatment. Two separate experiments were performed, and the methods and results will be discussed separately.

Experiment IIIa

Thirty-six male rats were randomly assigned to 4 dose groups of 9 animals each. The exposure levels of TET were 0, 5, 10 and 15 ppm. Since animals in Experiment II receiving the highest dose of TET, 20 ppm, developed hind limb paralysis, a 15 ppm TET dose was added in this experiment to specify the dose level at which paralysis develops. In this experiment, food consumption was also measured along with water consumption and body weight, to determine if decreased food intake contributed to the weight loss previously seen in TET-treated animals. TET was administered for 4 weeks, and open field activity and

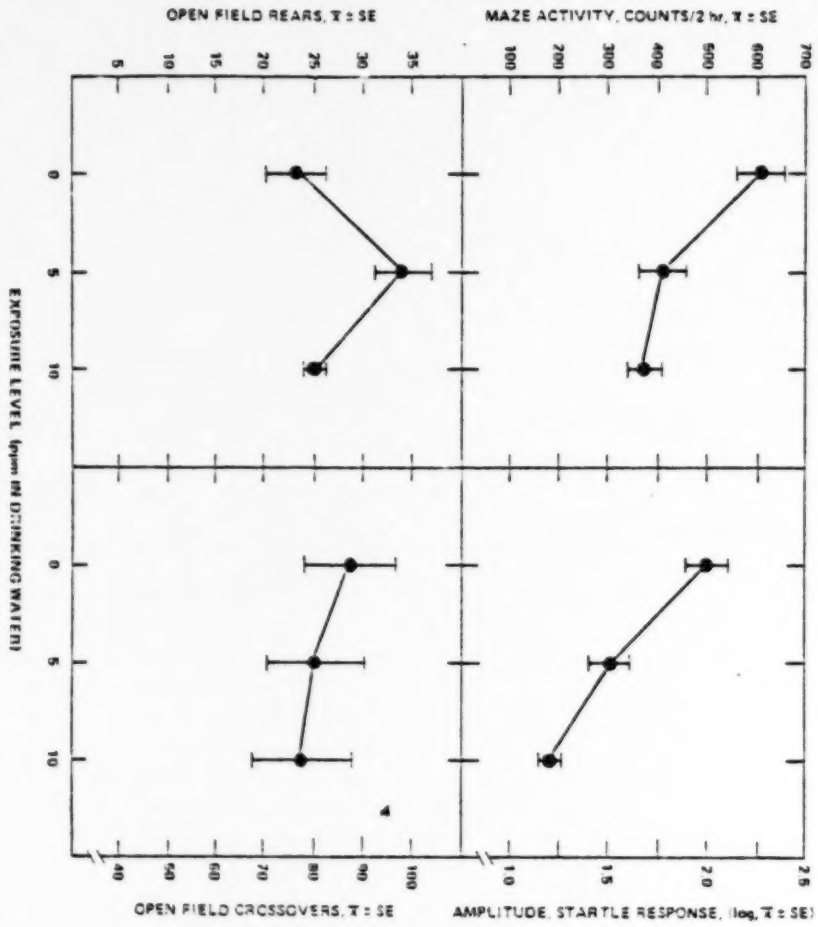
OPEN FIELD REARS, X̄ ± SE
MAZE ACTIVITY, COUNTS/2 hr, X̄ ± SE
EXPOSURE LEVEL (ppm IN DRINKING WATER)
OPEN FIELD CROSSOVERS, X̄ ± SE
AMPLITUDE, STARTLE RESPONSE, (log, X̄ ± SE)

FIGURE 2. Maze activity, startle response, and open field behavior (rears and crossovers) following subacute (3 week) exposure to TET in the drinking water (n = 6 per dose).

maze activity were tested on Days 23 and 24, respectively. All animals were sacrificed approximately one week following behavioral testing and body weights, brain, kidney and seminal vesicle weights were obtained.

Results

Table 4 shows water consumption, body weights, average daily dose of TET per week and total dose of TET during 3 weeks of exposure, combined for both studies in Experiment III. Water intake was reduced in TET-exposed

TABLE 2. Organ Weights (g) in Control and TET-Exposed Rats (N=6-9/Group). Data is Presented for Both Experiments II and III

Exposure Level (ppm)	0	5	10
Experiment II			
Liver	13.23±0.68	12.85±0.53	14.27±0.66
Brain	2.00±0.05	1.99±0.04	2.09±0.02
Adrenal ($x10^{-4}$)	47.17±3.41	40.40±2.20	41.67±2.11
Experiment III			
Kidney	3.26±0.06	3.41±0.11	3.27±0.11
Brain	2.04±0.02	2.11±0.03	2.26±0.03[1]
Wet Seminal vesicles	1.57±0.10	-	1.43±0.08

[1]Significantly different from control ($p<.01$).

animals; body weight gain was also reduced ($F(9,194)=79.7$, $p<.0001$). After 3 weeks of treatment animals receiving both 10 ppm ($p<.01$) and 15 ppm ($p<.01$) showed a significant reduction in body weight when compared to controls. Food consumption, measured in Experiment IIIa, was decreased by the third week of exposure in 10 ppm TET animals. While reduced water intake may reflect the aversiveness of the TET drinking water, the decrease in food consumption near the end of treatment in the 10 ppm animals probably represents a toxic effect of the TET itself. For both studies in this experiment, animals receiving 15 ppm TET developed hind limb paralysis. Since in the previous experiment animals had developed hind limb paralysis at 20 ppm TET, the threshold for paralysis under the present condition appears to be between 10 and 15 ppm TET.

Activity data in the maze and open field are shown in Fig. 3 for the 0, 5, and 10 ppm doses. Maze activity counts for the 2 hr test period differed significantly for dose groups ($F(2,24)=6.513$, $p<.006$); animals receiving 10 ppm were less active than either 0 ppm ($p<.01$) or 5 ppm ($p<.005$) animals. In

TABLE 3. Water Consumption, Body Weight, and Maze Activity (Mean±SE) in Control and Quinine-Control Rats (N=12 per Group)

Group	Week	Water Consumption (ml/Rat/Day)	Body Weight (g)	Maze Activity (Counts/2hr.)
Control	0	51±3	467±6	
	1	47±3	489±10	
	2	46±3	507±9	
	3	42±1	526±11	382±29
0.025% quinine	0	53±6	454±8	
	1	18±10	410±12	
	2	24±1	443±14	
	3	21±3	468±18	417±35

TABLE 4. Water Consumption, Body Weight, Average Daily Dose of TET per Week, Total Dose of TET (N=18 per Dose), and Food Consumption (N=9 per Dose) Following Subacute Exposure to TET in the Drinking Water (Mean ± SE)

Exposure Level	Week	Water Consumption (ml/Rat/Day)	Body Weight (g)	Mean Daily Dose/Week (mg/kg/Day)	Total Dose (mg/kg)	Food Consumption (g/Rat/Day)
0 ppm	0	-	416±3			-
	1	52±4	442±3	0		31±1
	2	51±5	463±4	0		35±2
	3	49±5	478±4	0	0	42±2
5 ppm	0	-	417±5	-		-
	1	37±2	444±5	0.42		29±2
	2	38±1	465±7	0.40		35±1
	3	46±2	474±8	0.51	9.3	38±1
10 ppm	0	-	418±4	-		-
	1	31±2	434±4	0.71		29±2
	2	35±3	450±5	0.76		31±4
	3	35±2	451±6	0.96	17.0	26±2
15 ppm	0	-	417±6	-		-
	1	22±1	427±5	0.77		22±2
	2(N=9)	16±2	404±6	0.60		15±1
	3[1]	48±2	415±7	-		31±3

[1]TET was removed from drinking water after week 2.

contrast to Experiment II, TET exposure significantly affected open field behavior. Crossovers in the open field differed between treatment groups ($F(2,24)=11.343$, $p<.0004$), as did rears ($F(2,24)=36.939$, $p<.0001$). In comparison to control animals, crossovers were reduced in both the 5 ppm ($p<.005$) and in the 10 ppm ($p<.001$) exposure groups. Rearing activity was also decreased in a dose-dependent manner: controls reared more than the 5 ppm exposure group ($p<.005$), and the 5 ppm group reared more than those receiving 10 ppm ($p<.001$).

Brain weight was significantly increased in experimental animals ($F(2,24)=14.179$, $p<.0001$) in a dose-dependent manner (Table 2). Brains from animals receiving 10 ppm TET weighed more than either those from the 0 ppm dose group ($p<.001$) or those from the 5 ppm dose group ($p<.001$). This increase in brain weight in the 10 ppm dose group is consistent with TET-induced brain edema. No treatment related differences were observed in either kidney or seminal vesicle weight.

Experiment IIIb

In the second part of this experiment, both emergence and recovery of TET toxicity were investigated. Thirty-six male rats were assigned to 4 dose groups of 9 animals each, that received doses of 0, 5, 10 or 15 ppm TET. Animals were tested for maze activity and landing foot-spread prior to exposure, then retested for both at the end of the first, second and third weeks of TET exposure.

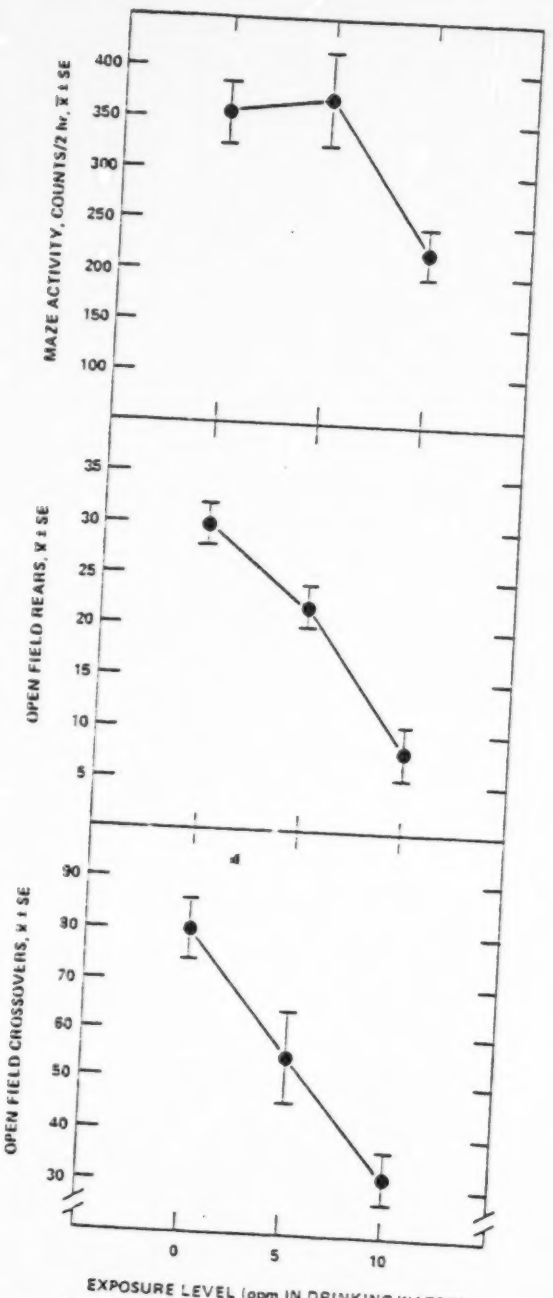

FIGURE 3. Maze activity, and open field behavior (rears and crossovers) following subacute (3 week) exposure to TET in the drinking water (N = 9 per dose).

Recovery of maze activity and landing foot-spread was evaluated at 2 and 4 weeks post-treatment.

Results

Activity data for the figure-eight maze are shown in Fig. 4. Because of the week to week variation in activity levels, $\log_{10}$ transformations were performed. As in Experiment IIIa, animals receiving 15 ppm TET developed hind limb paralysis and were not included in the behavioral testing. A MGLM analysis indicated a significant effect of treatment on activity ($F(12,38)=2.04$, $p<.047$); although there were no differences between groups in pretreatment maze activity, by week 3 of maze testing treatment groups differed in activity ($F(2,24)=4.107$, $p<.029$). Animals in both the 5 ppm and the 10 ppm TET exposure groups were less active than controls ($p<.05$) by the end of the third week of treatment. For maze activity there was also an interaction between week of testing and dose of TET ($F(10,40)=2.332$, $p<.028$); this interaction was significant between week 1 and week 2 of treatment ($F(2,24)=6.761$, $p<.005$). Maze activity did not differ significantly between groups at either 2 weeks or 4 weeks following discontinuation of TET.

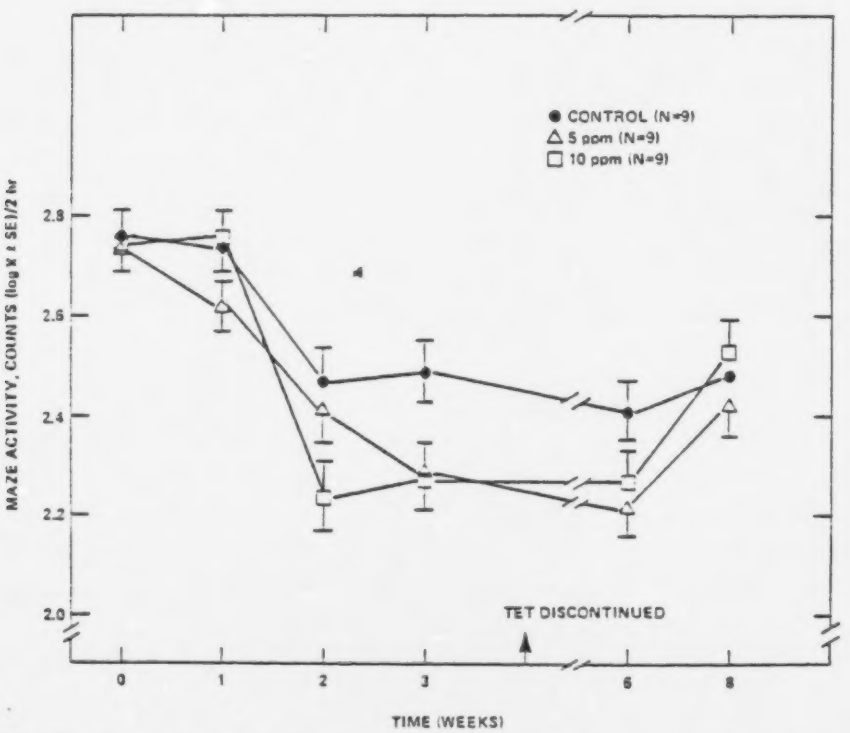

FIGURE 4. Maze activity in control and TET-exposed adult male rats tested weekly during exposure and at 2 week intervals during recovery. Dose administered in drinking water.

A significant effect of treatment was also found on the landing foot-spread as measured by the drop technique ($F(6,44)=3.275$, $p<.01$); data are shown in Fig. 5. The difference between groups in the landing foot-spread was significant both on week 2 ($F(2,24)=8.848$, $p<.001$) and on week 3 ($F(2,24)=6.052$, $p<.007$) of TET exposure. On week 2, animals in the 10 ppm dose group showed a narrower foot-spread than controls ($p<.01$), and on the third week, 10 ppm animals showed a narrower foot-spread than either controls ($p<.01$) or those in the 5 ppm dose group ($p<.05$). These data indicate that animals receiving the 10 ppm dose of TET showed impairment of neuromotor function as well as reduced locomotor activity. For the drop technique there was also an interaction between week of testing and dose of TET ($F(10,40)=4.049$, $p<.001$); this interaction was significant between week 1 and week 2 of treatment ($F(2,24)=4.657$, $p<.019$). By 2 weeks post-treatment, landing foot-spread still differed between treatment groups ($F(2,24)=3.817$, $p<.036$). Animals receiving 10 ppm TET showed a narrower foot-spread than controls ($p<.05$) but had recovered by 4 weeks after treatment.

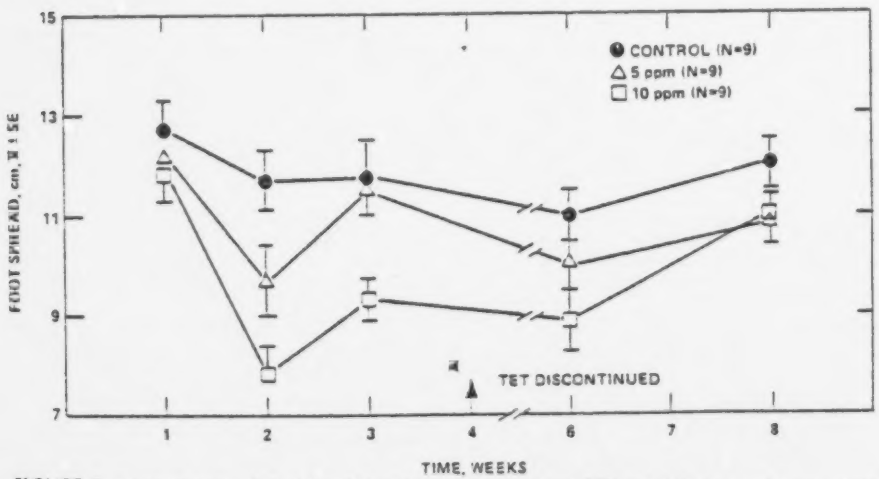

FIGURE 5. Measurement of "landing foot-spread" of control and TET-exposed adult male rats, tested weekly during exposure and at 2 week intervals during recovery. Dose administered in drinking water.

DISCUSSION

Rats exhibited hypoactivity when tested between 2 and 4 hr after acute administration of TET. This rapid behavioral change is consistent with the rapid distribution of TET. Rose and Aldridge (1968) reported that within 1 hr after a dose of 40μM of TET/kg, the brain contained 20 nM/g, of which 40% was recovered from the mitochondria. Glucose metabolism was also inhibited 2 hr after TET exposure, a time at which no measurable increase was observed in fluid content of the brain (Cremer, 1970). It is unlikely that the acute behavioral

mg/kg for 3 week subacute exposure. This study provides a first approximation of the threshold for the behavioral toxicity of TET. A more critical determination of threshold will require more extensive investigation including a more precise determination of dose.

These data also suggest that the behavioral effects of TET are independent of increases in brain weight. In Experiment II, hypoactivity occurred in the absence of brain edema. In both Experiment II and IIIb, 3 week exposure to 5 ppm TET produced a significant depression in maze activity whereas no significant increase in brain weight was observed. It should be noted, however, that the brain weights of the 5 ppm exposure group were increased over the control group, although this effect was not statistically significant. However, Marshall *et al.* (1976) reported an increased water content of brains from rats exposed for 4-5 weeks to 5 ppm TET.

It is interesting to note that the results of the landing foot-spread measurements are qualitively different from acrylamide exposure reported by Edwards and Parker (1977) and Jolecoeur *et al.* (1979). These investigators found that subacute exposure to acrylamide in the rat resulted in an increased foot-spread contrasted to the decrease observed in the present study. This qualitative difference may reflect the difference between axonopathy, produced by acrylamide (Fullerton, 1969) and myelinopathy, produced by TET. The apparent sensitivity of this test, combined with its simplicity, support its continued use as a potential screen for motor dysfunction.

Finally, these results indicate that the neuromotor effects of TET are largely reversible. Measurements of both motor activity and motor function (landing foot-spread) return to control levels within 1 month after discontinuation of exposure. This behavioral recovery agrees with the morphological recovery described by Magee *et al.* (1957).

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